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Develop and Validate a Risk Score in Predicting Renal Failure in Focal Segmental Glomerulosclerosis

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Keywords
Focal segmental glomerulosclerosis · Clinicopathological features · Survival analysis · Predictive model

Abstract
Introduction: The aim of this study was to develop and validate a risk score (RS) for end-stage kidney disease (ESKD) in patients with focal segmental glomerulosclerosis (FSGS). ***Methods:*** Patient with biopsy-proven FSGS was enrolled. All the patients were allocated 1:1 to the two groups according to their baseline gender, age, and baseline creatinine level by using a stratified randomization method. ESKD was the primary endpoint. ***Results:*** We recruited 359 FSGS patients, and 177 subjects were assigned to group 1 and 182 to group 2. The clinicopathological variables were similar between two groups. There were 23 (13%) subjects reached to ESKD in group 1 and 22 (12.1%) in group 2. By multivariate Cox regression analyses, we established RS 1 and RS 2 in groups 1 and 2, respectively. RS 1 consists of five parameters including lower eGFR, higher urine protein, MAP, IgG level, and tubulointerstitial lesion (TIL) score; RS 2 also consists of five predictors including lower C3, higher MAP, IgG level, hemoglobin, and TIL score. RS 1 and RS 2 were cross-validated between these two groups, showing RS 1 had better performance in predicting 5-year ESKD in group 1 (c statics, 0.86 [0.74–0.98] vs. 0.82 [0.69–0.95]) and group 2 (c statics, 0.91 [0.83–0.99] vs. 0.89 [0.79–0.99]) compared to RS 2. We then stratified the risk factors into four groups, and Kaplan-Meier survival curve revealed that patients progressed to ESKD increased as risk levels increased. ***Conclusions:*** A predictive model incorporated clinicopathological feature was developed and validated for the prediction of ESKD in FSGS patients.

Introduction

Focal segmental glomerulosclerosis (FSGS) is one of the most common glomerular diseases that leads to end-stage kidney disease (ESKD) worldwide [1–3]. Clinical features of FSGS include nephrotic syndrome (NS) and non-nephrotic range of proteinuria, accompanied by hematuria, hypertension, and impaired renal function [1]. FSGS represents a renal histologic lesion with diverse etiologies that are caused by podocyte injury [4, 5]. Accordingly, the clinical features and prognosis of FSGS are quite

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heterogeneous. To better understand the heterogeneous nature of FSGS disease, KDIGO 2021 guideline recommended that FSGS is reclassified into four types: primary FSGS (PFSGS), genetic FSGS, secondary FSGS, and FSGS-undetermined cause (UC) [6].

Incidence of progression to ESKD in patients with FSGS has been increasing recently. McGrogan et al. [7] reported that annual incidence rates of FSGS ranged from 0.2 to 1.8/100,000 population per year. The incidence of FSGS is about 5 times higher in black patients than that in white patients, with an annual incidence of 2.4 to 0.5/100,000, respectively, in the USA [2], which is likely due to the increased presence of 2 variants of apolipoprotein L1 in black patients [8]. In China, the incidence rate of FSGS among all renal biopsied samples in a large hospital increased from 6% to 7.34% from 1979 to 2014 [9]. Xie et al. [10] reported that prevalence of FSGS in China varies by geographical region, with prevalence of FSGS much higher in south than in north, suggesting potential differences in its pathogenesis. Incidence rate of reaching ESKD attributed to FSGS has been recently increased. Thomas et al. [11] reported that 28% of FSGS patients reached ESKD after a median of 1.8-year follow-up. Presence of large amount of proteinuria (>3.0–3.5 g/day) was shown to be associated with poor renal outcome with 50% of PFSGS patients reached to ESKD over 6–8 years [12]. In addition, prognosis of patients with FSGS varies depending on the response to treatment. Previous studies reported that FSGS patients reaching and maintaining a complete remission of proteinuria rarely progress to ESKD [13–15]. Micky et al. [16] reported that 10-year renal survival rate was 92% if FSGS patients achieved partial or complete remission of proteinuria after treatment, whereas renal survival rate was only 33% if they did not respond to treatment. A recent study showed that incremental proteinuria reduction was also important with even modest reductions in proteinuria (i.e., 20–30% reduction) associated with improving estimated glomerular filtration rate (eGFR) of >1–2 mL/year [17]. Furthermore, they reported that baseline renal function and proteinuria level were strongly associated with prognosis [16]. The prognosis of FSGS patients was even worse if they carried genetic mutations [18].

The Columbia classification of FSGS was proposed to better reflect patients' clinical severity and response to treatment [19, 20]. This FSGS classification subdivides the lesion of FSGS into five histological variants: collapsing, cellular, tip, perihilar, and not otherwise specified. D'Agati et al. [19] reported that the tip variant had strong association with white race, milder pathologic injury, and lowest risk for progression, whereas collapsing variant was common in blacks and exhibited severe clinical manifestations with highest progressive rate. However, a recent study from Kawaguchi et al. [21] reported that renal outcome was similar among the variants suggesting that FSGS variants alone might not have significant impacts on the renal outcome. In addition, chronic tubule-interstitial injury score was found to independently affect progression to ESKD [22]. Severe tubulointerstitial lesion (TIL) was found to be associated with poor renal outcome [23, 24]. Mariani et al. [25] reported that the degrees of TIL were associated with risk of eGFR decline across different types of proteinuric glomerulopathy including FSGS based on patients enrolled in Nephrotic Syndrome Study Network (NEPTUNE), suggesting these pathological parameters had potential value in predicting risk of progression in FSGS patients [25, 26].

Despite significant progress having been made in assessing the clinical outcome of FSGS patients using traditional risk factors, FSGS patients with different variants differ noticeably in management and prognosis in the clinical setting. There is still lack of a risk score (RS) to accurately predict renal outcome in patients with FSGS by combining all the independent clinicopathological risk factors. In this study, we developed and validated a RS for FSGS progression by combining all independent risk factors based on a large of cohort of biopsy-proven FSGS patients in our hospital.

Methods

Study Design and Population

This study consisted of a cohort of data from patients that underwent renal biopsy at the Ruijin Hospital from January 1997 to December 2021. A total of 440 patients diagnosed with FSGS by renal biopsy were screened, and 359 patients were eligible for this study. Inclusion criteria include (1) any age biopsied-proved FSGS; (2) eGFR >15 mL/min/1.73 m^2; (3) follow-up at Ruijin Hospital. Patients were excluded from this study if patients had already reached to ESKD, patients were known to be secondary FSGS caused by obesity, hypertension, viral infection, and autoimmune diseases, and patients had incomplete clinical or pathological data. Enrolled patients were divided into two groups randomly, the discovery group and the validation group, by using stratified sampling based on age, gender and baseline creatinine level, for further analysis [6].

Clinical and Laboratory Data

Clinical information was collected for all patients including age, gender, medical history including hypertension and diabetes, use of medications, family history, BMI, systolic and diastolic blood pressures, and mean arterial pressure (MAP). Laboratory data were collected including serum creatinine (Scr), serum albumin, uric acid, eGFR (using the CKD-EPI formula), total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, lipoprotein a, serum calcium (Ca), serum phosphorus, immunoglobin G (IgG), immunoglobin A, immunoglobin M, complement 3 (C3),

complement 4, white blood cell count, hemoglobin (Hb), hematocrit, platelet, and 24-h proteinuria (urine protein [UP]). Renal endpoints analyzed in this study were ESKD defined as initiation of renal replacement therapy, or eGFR reached <15 mL/min/1.73 m^2.

Renal Biopsy Data

Renal biopsy was conducted for all screened 440 patients who were followed by our nephrology department at Ruijin Hospital. Indications for renal biopsy were decided by the nephrologists who cared for these patients based on their clinical manifestations including proteinuria, hematuria, and renal function. All biopsy samples were used to prepare 3-μm sections that were used for periodic acid-Schiff, Masson's trichrome, and hematoxylin and eosin staining. Two pathologists independently reviewed all samples. The extents of TILs and classifications of FSGS were determined by pathologists based on the standard criteria [19, 27]. TIL was scored based on tubular atrophy, interstitial fibrosis, and interstitial inflammation which was graded semiquantitatively on a scale of 0–3+ depending on the extent and severity of the lesion. TIL grading was based on the sum of 3 pathological indicators: a total score of zero was defined as grade 0, 1–3 was grade 1, 4–6 was grade 2, and 7–9 was grade 3 [22, 28].

Statistical Analyses

Categorical data were given as frequencies (percentages), while continuous data were given as mean ± SD and median with interquartile range, respectively. Shapiro-Wilks test for normality was used to detect any departure from normality. Categorical data were compared using Pearson's χ^2 test. Normally and non-normally distributed continuous data were compared using Student's *t* test and Mann-Whitney U test, respectively. Kaplan-Meier (KM) curves were used to analyze cumulative renal survival, with comparisons between groups being made via the log-rank test. Independent predictors of renal outcomes were selected using the univariate and multivariate Cox proportional hazard regression model approach that was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

The results of above analysis were then utilized to guide the construction of a predictive model using backward selection to analyze the odds of reaching the renal endpoint within 3 and 5 years. The predictive performance of derived model was analyzed using calibration curves and area under curve (AUC) values. The predictive model was internally validated through analyzing two groups of cohorts. A 2-sided $p < 0.05$ was the significance threshold. SPSS 21.0 (SPSS Inc., Chicago, IL, USA), R v.4.1.2 (http://www.R-porject.org/), dyn v0.2-9.6, rms v6.2-0, pec v2021.10.11, pROC v1.18.0, readr v2.1.1, glmnet v4.1-3, readxl v1.3.1, glmulti v1.0.8, MatchIt v4.3.2, prodlim v2019.11.13, timeROC v0.4, sampling v2.9, survival v3.2-13, tableone v0.13.0, lubridate v1.8.0, survminer v0.4.9, tidyverse v1.3.1, forestplot v2.0.1, My.stepwise v0.1.0 packages were used for all statistical testing.

Results

Patient Baseline Characteristics

A total of 440 patients were screened during the study, and 359 patients were included for analysis of this study (Fig. 1). Baseline demographic, laboratory, and clinical data are shown in Table 1. The 359 patients were enrolled for analysis with 151 female subjects accounting for 42.1%. The mean age at renal biopsy was 40.1 ± 15.8. Follow-up times were from 0.7 month to 206 months, with median follow-up time of 38 months. Baseline characteristics revealed the median 24-h UP of 1.9 g/24 h with median eGFR of 73 mL/min/1.73 m^2. One hundred thirty-six subjects (37.9%) were diagnosed as CKD stage 3 or stage 4 upon renal biopsy. During the period of the follow-up, 45 subjects progressed to ESKD, accounting for 12.5%.

Identifying Risk Factors for Predicting ESKD in FSGS Patients

To analyze the risk factors contributing the renal endpoint, we did univariate Cox analysis. As shown in Table 1, we found that the following risk factors were associated with disease progressive and worse prognosis including higher Scr (HR = 1.005, 95% CI 1.002–1.01, $p < 0.01$), lower eGFR (HR = 0.98, 95% CI 0.97–0.99, $p < 0.001$), reaching CKD stage 3 upon renal biopsy (HR = 3.41, 95% CI 1.81–6.43, $p < 0.001$), elevated MAP (HR = 1.03, 95% CI 1.004–1.05, $p < 0.05$), history of hypertension (HR = 2.60, 95% CI 1.44–4.71, $p < 0.01$), higher uric acid (HR = 1.004, 95% CI 1.001–1.01, $p < 0.01$), lower cholesterol level (HR = 0.86, 95% CI 0.74–0.98, $p < 0.05$), lower high-density lipoprotein level (HR = 0.27, 95% CI 0.12–0.61, $p < 0.01$), lower low-density lipoprotein level (HR = 0.80, 95% CI 0.66–0.97, $p < 0.05$), higher Ca level (HR = 7.57, 95% CI 1.07–53.56, $p < 0.05$), higher phosphorous level (HR = 1.69, 95% CI 1.10–2.62, $p < 0.05$), higher calcium phosphate product (HR = 1.40, 95% CI 1.11–1.76, $p < 0.01$), higher complement 4 level (HR = 1.01, 95% CI 1.005–1.02, $p < 0.01$), and higher TIL score (HR = 2.92, 5% CI 1.84–4.64, $p < 0.001$).

Establishing the Predictive Model for ESKD in Two Groups of Cohorts

Due to the limited sample size, we decided randomly to assign 359 subjects into group 1 and group 2, establish the RS 1 and RS 2, respectively, and cross-validate the RSs to improve the reliability of the risk models. We first randomly assigned all FSGS subjects into two groups of cohorts in one-to-one ratio based on age, gender, and baseline creatinine level. We then established and validated RS in predicting ESKD. As shown in Table 2, there were 177 subjects assigned to group 1 cohort, whereas 182 subjects were assigned to group 2 cohort. There was no significant difference between two groups in major risk factors including age upon renal biopsy, follow-up time,

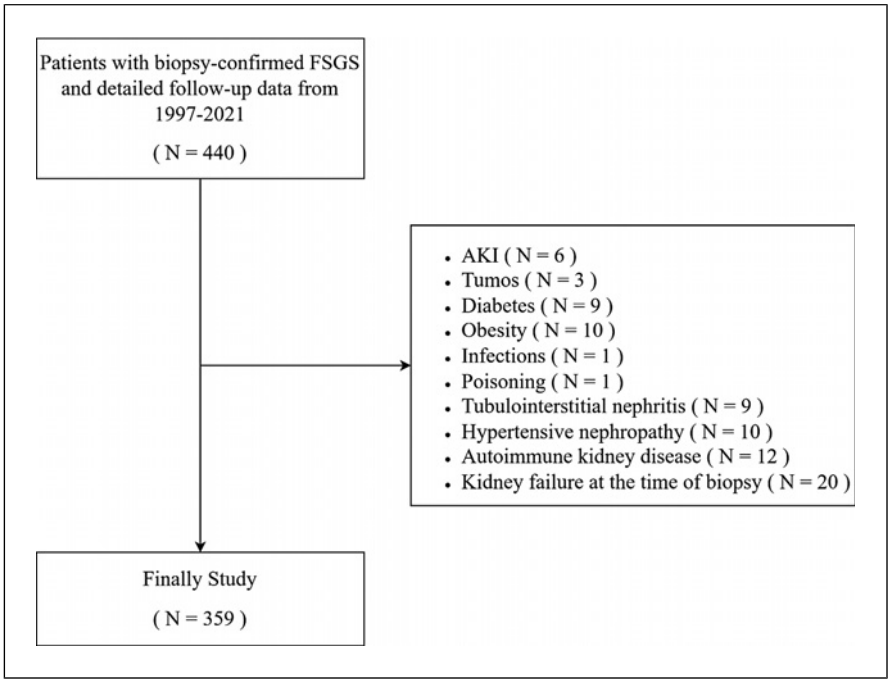

Fig. 1. Flowchart of cohort selection. AKI, acute kidney injury; FSGS, focal segmental glomerulosclerosis.

TIL score, history of hypertension, Scr, baseline CKD 3 ($p > 0.05$), ratio of FSGS-UC to PFSGS, and incidence of renal endpoint event ($p > 0.05$).

Using multivariate Cox regression, we first established RSs for disease progression, RS 1 and RS 2, based on the regression coefficients for the independent predictors retained in the best models for group 1 and group 2, respectively. As shown in Table 3, 4, RS 1 equation contained five predictors including eGFR, UP, MAP, serum IgG, and TIL score, whereas RS 2 is provided by the formula containing five predictors including MAP, serum IgG, C3, Hb, and TIL score. RS 1 indicated that the following risk factors including lower eGFR (HR = 0.96, 95% CI 0.93–0.99), higher UP (log UP, HR = 15.04, 95% CI 2.03–111.28), higher MAP (HR = 1.07, 95% CI 1.03–1.13), higher IgG level (HR = 1.002, 95% CI 1.001–1.003), and higher TIL score (HR = 4.53, 95% CI 1.89–10.90) were associated with progressive disease, whereas RS 2 suggested that risk factors including higher MAP (HR = 1.11, 95% CI 1.05–1.17), higher IgG level (HR = 1.005, 95% CI 1.002–1.01), lower C3 (HR = 0.92, 95% CI 0.88–0.96), higher Hb (HR = 1.02, 95% 0.99–1.05), and higher TIL score (HR = 5.51, 95% CI 1.99–15.25) were associated with disease progression.

As shown in Table 3, RS 1 showed that lower eGFR (HR = 0.96, 95% CI 0.93–0.99), higher MAP (HR = 1.05, 95% CI 1.01–1.10), and higher IgG level (HR = 1.002, 95% CI 1.001–1.003) were also risk factors for disease progression in group 2, whereas RS 2 showed that higher MAP (HR = 1.06, 95% CI 1.02–1.10) and higher TIL score (HR = 4.05, 95% CI 1.85–8.86) were the risk factors for disease progression in group 1. Two formulae for RS 1 and RS 2 are shown below:

RS 1 = −0.01*eGFR [mL/min/1.73 m^2] + 2.71*UP [log UP, g/24 h] + 0.07*MAP [mm Hg] + 0.002*IgG [mg/dL] + 1.51*TIL.

RS 2 = 0.10*MAP [mm Hg] + 0.005*IgG [mg/dL] − 0.08*C3 [mg/dL] + 0.02*Hb [g/L] + 1.71*TIL.

Evaluating Performance of Predictive Models for ESKD

We then evaluated the performance of the RS in predicting renal endpoint, ESKD in 3 and 5 years, respectively. We compared the performances of RS in 3-year and 5-year predictions of ESKD among group 1, group 2, and whole cohort. As shown in Table 4, compared to RS 2, RS 1 had better overall performance in predicting 3-year ESKD (R^2 0.82 vs. 0.71) and 5-year ESKD (R^2 0.82 vs. 0.71) in whole cohort. Survival receiver operating characteristic (ROC) analysis revealed that the RS 1 provided considerably improved discriminative power at 3-year and 5-year follow-up compared to RS 2. The area under the survival ROC curve of RS 1 was higher than that of RS 2 for 3-year ESKD prediction (0.95 [95% CI 0.89–0.99] vs. 0.90 [95% CI 0.81–0.99]) and 5-year ESKD prediction (0.86 [95% CI 0.76–0.96] vs. 0.85 [95% CI 0.76–0.94]) in whole cohort. We also compared RS 1 predictive model to RS 2

Table 1. Characteristic and Cox analysis of all enrolled FSGS patients

	All patients (N = 359)	HR (95% CI)
Age at biopsy, years	40.1±15.8	1.01 (0.99–1.03)
Females, *n* (%)	151 (42.1)	0.63 (0.34–1.16)
Follow-up time, months	38 [15–88]	
Scr, μmol/L	96 [69–145]	**1.005 (1.002–1.01)****
eGFR, mL/min/1.73 m^2	73 [46–106]	**0.98 (0.97–0.99)*****
CKD3 at baseline, *n* (%)	136 (37.9)	**3.41 (1.81–6.43)*****
UP, g/24 h	1.9 [0.9–3.9]	0.99 (0.99–1.0001)
LogUP	0.28 [−0.02–0.59]	1.56 (0.86–2.83)
BMI, kg/m^2	23.9±3.6	1.03 (0.94–1.13)
MAP, mm Hg	96.8±13.1	**1.03 (1.004–1.05)***
History of hypertension, *n* (%)	143 (39.8)	**2.60 (1.44–4.71)****
History of diabetes, *n* (%)	13 (3.6)	0.01 (0.001–9.99)
Total protein, g/L	55.6±13.1	1.02 (0.996–1.05)
Alb, g/L	33 [20–38]	1.03 (0.99–1.06)
UA, μmol/L	374 [308–458]	**1.004 (1.001–1.01)****
Cholesterol, mmol/L	7.2±4.6	**0.86 (0.74–0.98)***
Triglycerides, mmol/L	2.3 [1.5–3.3]	1.05 (0.91–1.2)
HDL, mmol/L	1.4±0.5	**0.27 (0.12–0.61)****
LDL, mmol/L	4.4±2.7	**0.80 (0.66–0.97)***
LP(a), g/L	0.3 [0.1–0.6]	0.48 (0.19–1.25)
Ca, mmol/L	2.1±0.2	**7.57 (1.07–53.56)***
P, mmol/L	1.3±0.4	**1.69 (1.10–2.62)***
Ca × P, $mmol^2/L^2$	2.8±0.7	**1.40 (1.11–1.76)****
IgG, mg/dL	953±440	1.0004 (0.99–1.001)
IgA, mg/dL	224 [165–323]	1.002 (0.99–1.004)
IgM, mg/dL	130 [91–181]	0.999 (0.99–1.002)
C3, mg/dL	112.7±32.6	0.99 (0.98–1.01)
C4, mg/dL	25 [20.9–31]	**1.01 (1.005–1.02)****
WBC, $\times 10^9$/L	7.9±3.1	1.02 (0.92–1.14)
Hb, g/L	132.7±20.9	0.997 (0.98–1.01)
HCT, %	38.8±6.6	0.97 (0.93–1.02)
PLT, $\times 10^9$/L	229.9±77.2	1.0001 (0.99–1.004)
TIL, *n* (%)		
0	55 (15.3)	**2.92 (1.84–4.64)*****
1	129 (35.9)	
2	154 (42.9)	
3	21 (5.8)	
RAAS blocker use, *n* (%)	212 (59.1)	1.60 (0.85–3.00)
Immunosuppressor use, *n* (%)	237 (66.0)	0.77 (0.43–1.40)
End point: ESKD, *n* (%)	45 (12.5)	

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. Scr, serum creatinine; eGFR, estimated glomerular filtration rate; CKD3, chronic kidney disease stage III; UP, urine protein; LogUP, log urine protein base 10; BMI, body mass index; MAP, mean arterial pressure; Alb, albumin; UA, uric acid; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LP(a), lipoprotein(a); Ca × P, calcium phosphate product; WBC, white blood cell count; HCT, hematocrit; PLT, platelet; TIL, tubulointerstitial lesion; RAAS, renin-angiotensin-aldosterone system; ESKD, end-stage kidney disease.

predictive model in group 1 patient to generate ROC curve to estimate discrimination of the 3-year risk and 5-year risk for ESKD as shown in Figure 2a, b, respectively. These data confirmed that RS 1 is better predictive model than RS 2 in predicting risk factors for progression to ESKD with good discrimination ability. Using our group 1 and group 2 samples, we further compared the predicted risk versus observed rate of ESKD at 5 years [29]. As shown in Figure 3, the discriminative slope calculated as the difference between the mean predicted probabilities was similar between group 1 and group 2 (0.19 vs. 0.17) using RS

Table 2. Characteristic of different groups

	Group 1 (*N* = 177)	Group 2 (*N* = 182)	*p* value
Age at biopsy, years	40.1±15.8	40.1±15.8	0.99
Females, *n* (%)	74 (41.8)	77 (42.3)	0.99
Follow-up time, months	34 [14–85]	46 [16–93]	0.09
FSGS-UC, *n* (%)	99 (55.9)	105 (57.7)	0.82
Scr, μmol/L	93 [69–149]	101 [69–141]	0.82
eGFR, mL/min/1.73 m^2	79 [45–106]	69 [48–106]	0.83
CKD3 at baseline, *n* (%)	66 (37.3)	70 (38.5)	0.90
UP, g/24 h	2.0 [1.1–3.9]	1.9 [0.9–3.8]	0.99
LogUP	0.29 [0.03–0.59]	0.28 [−0.06–0.58]	0.46
BMI, kg/m^2	24.2±3.5	23.6±3.6	0.16
MAP, mm Hg	97.0±13.8	96.7±12.5	0.86
History of hypertension, *n* (%)	76 (42.9)	67 (36.8)	0.34
History of diabetes, *n* (%)	6 (3.4)	7 (3.8)	0.73
Total protein, g/L	55.7±13	55.6±13.2	0.94
Alb, g/L	33 [21–38]	33 [19–38]	0.64
UA, μmol/L	377 [313–468]	365 [303–445]	0.07
Cholesterol, mmol/L	7.5±5.6	6.9±3.4	0.23
Triglycerides, mmol/L	2.3 [1.6–3.3]	2.3 [1.5–3.3]	0.26
HDL, mmol/L	1.4±0.6	1.4±0.5	0.33
LDL, mmol/L	4.4±2.7	4.4±2.7	0.96
LP(a), g/L	0.3 [0.1–0.5]	0.3 [0.1–0.6]	0.44
Ca, mmol/L	2.1±0.2	2.1±0.2	0.76
P, mmol/L	1.3±0.3	1.4±0.5	0.15
Ca × P, $mmol^2/L^2$	2.8±0.6	2.9±0.9	0.24
IgG, mg/dL	951±393.5	955.6±478	0.93
IgA, mg/dL	233 [179–332]	216 [155–321]	0.32
IgM, mg/dL	136 [99–185]	126 [84–173]	0.67
C3, mg/dL	116±32.2	109.7±32.9	0.09
C4, mg/dL	26 [21–33]	25 [20–30]	0.68
WBC, $\times 10^9$/L	8.1±3.1	7.6±3.1	0.11
Hb, g/L	132.8±21.8	132.6±20	0.93
HCT, %	39±5.9	38.6±7.3	0.58
PLT, $\times 10^9$/L	239±69.9	221.2±82.8	**0.03**
TIL, *n* (%)			
0	27 (15.3)	28 (15.4)	0.70
1	59 (33.3)	70 (38.5)	
2	79 (44.6)	75 (41.2)	
3	12 (6.8)	9 (4.9)	
RAAS blocker use, *n* (%)	104 (58.8)	108 (59.3)	0.99
Immunosuppressor use, *n* (%)	119 (67.2)	118 (64.8)	0.71
End point: ESKD, *n* (%)	23 (13)	22 (12.1)	0.92

FSGS-UC, FSGS of undetermined cause; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; CKD3, chronic kidney disease stage III; UP, urine protein; LogUP, log urine protein base 10; BMI, body mass index; MAP, mean arterial pressure; Alb, albumin; UA, uric acid; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LP(a), lipoprotein(a); Ca × P, calcium phosphate product; WBC, white blood cell count; Hb, hemoglobin; HCT, hematocrit; PLT, platelet; TIL, tubulointerstitial lesion.

1 model as well as between group 1 and group 2 (0.11 vs. 0.13) using RS 2 model. Overall, the calibrated performance of RS 1 model in predicting the risks for ESKD events compared to non-ESKD in these two groups was better than that of RS 2 model.

Clinical Utility of the Predicted Model

From above analysis, we chose RS 1 as final predictive model and calibrated RS 1 model in group 2 cohort. Based on the predictive results, we stratified FSGS patients into four risk groups: low risk (<16th), intermediate risk

Table 3. Establish ESKD prediction models in two groups using multivariate Cox regression

	Group 1		Group 2	
	HR 95% CI	*p* value	HR 95% CI	*p* value
RS 1				
eGFR, mL/min/1.73 m^2	0.99 (0.97–1.002)	0.09	0.96 (0.93–0.99)	**0.01**
LogUP	15.04 (2.03–111.28)	**0.01**	3.02 (0.88–10.45)	0.08
MAP, mm Hg	1.07 (1.03–1.13)	<**0.01**	1.05 (1.01–1.10)	**0.046**
IgG, mg/dL	1.002 (1.001–1.003)	**0.01**	1.002 (1.001–1.003)	<**0.01**
TIL, *n* (%)	4.53 (1.89–10.90)	<**0.01**	3.00 (0.92–9.75)	0.07
RS 2				
MAP, mm Hg	1.06 (1.02–1.10)	<**0.01**	1.11 (1.05–1.17)	<**0.01**
IgG, mg/dL	1.001 (0.99–1.003)	0.06	1.005 (1.002–1.01)	<**0.01**
C3, mg/dL	1.01 (0.99–1.02)	0.62	0.92 (0.88–0.96)	<**0.01**
Hb, g/L	0.99 (0.97–1.02)	0.72	1.02 (0.99–1.05)	0.15
TIL, *n* (%)	4.05 (1.85–8.86)	<**0.01**	5.51 (1.99–15.25)	<**0.01**

RS 1, best model derived from group 1; RS 2, best model derived from group 2; eGFR, estimated glomerular filtration rate; LogUP, log urine protein base 10; MAP, mean arterial pressure; Hb, hemoglobin; TIL, tubulointerstitial lesion.

Table 4. Performance of RS 1 and RS 2 in different groups of cohort

	RS 1		RS 2	
	AUC (95% CI)	R^2	AUC (95% CI)	R^2
3-year ESKD				
Group 1	0.95 (0.91–0.99)	0.84	0.87 (0.75–0.99)	0.70
Group 2	0.96 (0.93–0.99)	0.87	0.97 (0.95–0.99)	0.91
Total	0.95 (0.89–0.99)	0.82	0.90 (0.81–0.99)	0.71
5-year ESKD				
Group 1	0.86 (0.74–0.98)	0.84	0.82 (0.69–0.95)	0.70
Group 2	0.91 (0.83–0.99)	0.87	0.89 (0.79–0.99)	0.91
Total	0.86 (0.76–0.96)	0.82	0.85 (0.76–0.94)	0.71
RS 1: −0.01*eGFR + 2.71*LogUP + 0.07*MAP + 0.002*IgG + 1.51*TIL				
RS 2: 0.10*MAP + 0.005*IgG − 0.08*C3 + 0.20*Hb + 1.70*TIL				

RS 1, Best model derived from Group 1; RS 2, Best model derived from Group 2. Total represents whole cohort of present study.

(16–50th), higher risk (50–84th), and highest risk (>84th) according to previously reported cut-off values [30, 31]. We further analyzed the renal endpoint events in different ESKD risk groups. As shown in Figure 4a, KM curves among different risk groups were well separated (overall $p < 0.0001$), suggesting the excellent discrimination ability for patients with different risk levels. KM curves revealed that there were no patients in the low risk group developed ESKD, and the median renal survival times in years are 7.46 versus 13.19 between highest risk group and higher risk group ($p < 0.01$), 7.46 versus 14.5 between highest risk group and intermediate risk group ($p < 0.01$), and 13.19 versus 14.5 between high risk group and low risk group ($p < 0.01$). Difference in median survival time is also dramatically significant ($p < 0.01$). These data suggested that RS 1 model can accurately predict the prognosis on renal survival in patients with FSGS.

We next evaluated the association between RS 1 and the estimated risk of progression to ESKD by subgroups defined by age (younger or older than 60 years old), gender, FSGS classification (PFSGS or FSGS-UC), CKD stage (stage I-II or III-IV), NS (with or without NS), renin-angiotensin-aldosterone system blockage (use or not use), and immunosuppressive agents (use or not use). As shown in Figure 4b, we found the estimated risk of ESKD was similar in these subgroups. These results suggested that the

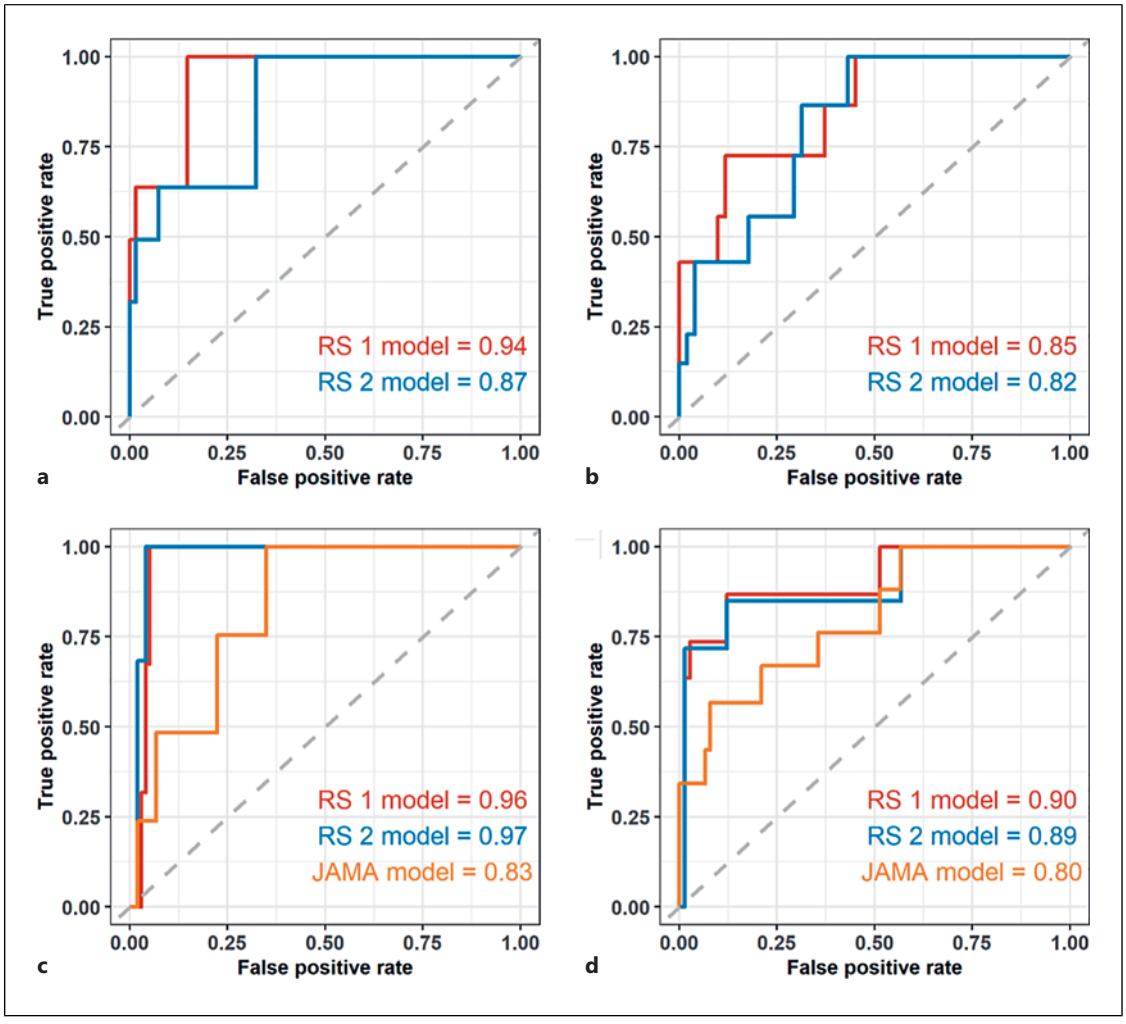

Fig. 2. ROC analysis for groups 1 and 2 using RS 1 or RS 2 models and JAMA model. **a** ROC curve analysis of 3-year risk for group 1 using RS 1 and RS 2 models. **b** ROC curve analysis of 5-year risk for group 1 using RS 1 and RS 2 models. **c** ROC curve analysis of 3-year risk for group 2 using RS 1, RS 2, and JAMA models. **d** ROC curve analysis of 5-year risk for group 2 using RS 1, RS 2, and JAMA models. ROC, receiver operating characteristic; RS 1, best model derived from group 1; RS 2, best model derived from group 2.

association between RS 1 and the estimated risk of ESKD was independent to all these confounding factors, suggesting RS 1 provided physician a proper tool to guide their clinical managements for FSGS patients.

Comparison to Existing Model

Finally, we also compared our predictive models RS 1 and RS 2 to existing CKD predictive model (JAMA model) by Tangri et al. [32] published in JAMA, in which a predictive model for progression of CKD to kidney failure was developed using demographic, clinical, and laboratory data from two independent Canadian cohorts. We did ROC curve analysis for group 2 patients using RS 1, RS 2, and JAMA model, respectively. Compared to the JAMA predictive model, both RS 1 and RS 2 showed an increase on the discriminative ability for 3-year risk prediction (RS 1 of 0.96 [0.93–0.99] and RS 2 of 0.97 [0.95–0.99] vs. 0.83 [0.70–0.96]) in Figure 2c and for 5-year risk prediction (RS 1 of 0.91 [0.83–0.99] and RS 2 of 0.89 [0.79–0.99] vs. 0.80 [0.65–0.95]) in Figure 2d and Table 4, suggesting that RS 1 and RS 2 from the present study are the better models for predicting the risks for ESKD at 3 years and 5 years.

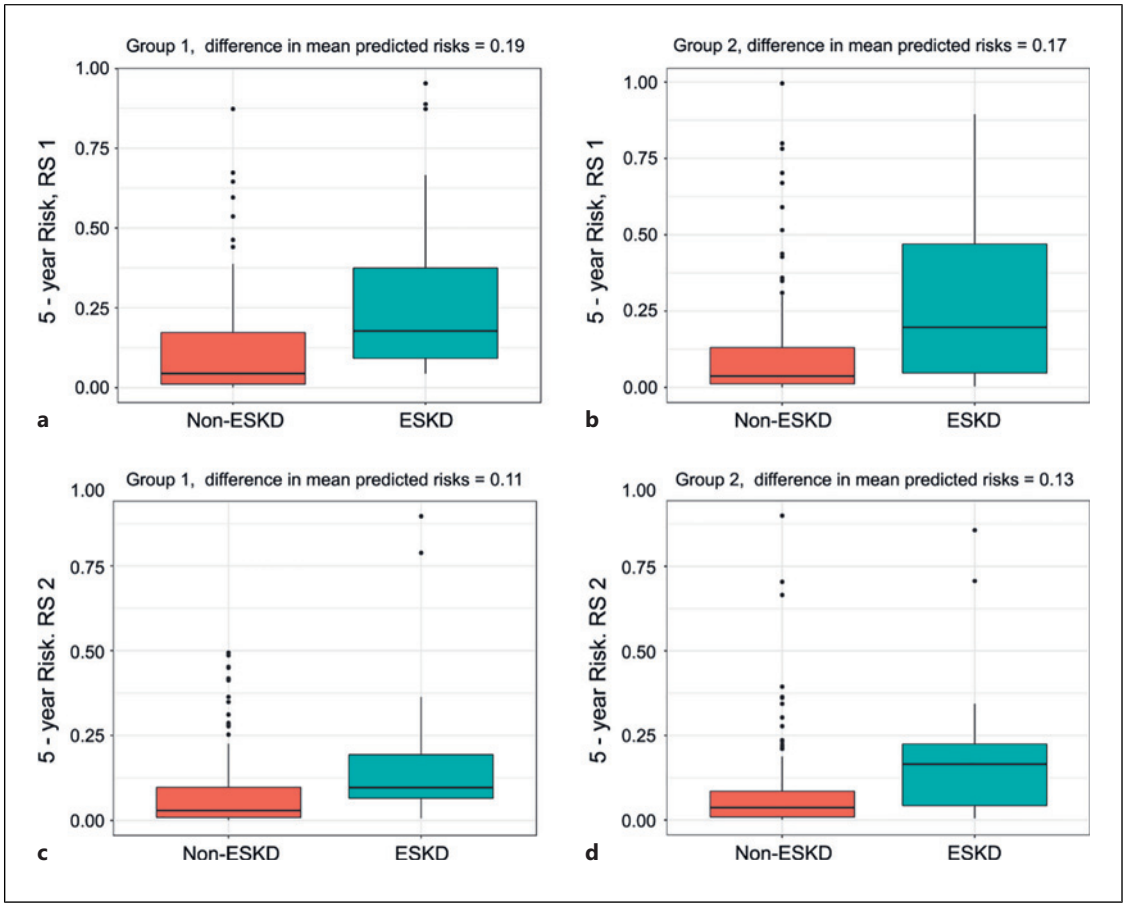

Fig. 3. Box plots of predicted end-stage kidney disease (ESKD) risks. Box plots of predicted ESKD risk calculated using the RS 1 (best model from group 1) or RS 2 (best model from group 2) between non-ESKD or ESKD patients with focal segmental glomerulosclerosis (FSGS) at 5-year follow-up. **a** Group 1, ESKD risk calculated using the RS 1. **b** Group 2, ESKD risk calculated using the RS 1. **c** Group 1, ESKD risk calculated using the RS 2. **d** Group 2, ESKD risk calculated using the RS 2. The difference in mean predicted risks (discrimination slope) is calculated as the difference between the mean predicted risks between patients with FSGS with or without ESKD at 5-year follow-up.

Discussion

In the present study, we analyzed the clinicopathological features of FSGS patients and their association with renal endpoint outcomes in our cohort of biopsy-proven FSGS patients [6]. Using multivariate Cox regression analysis, we established the RSs (RS 1 and RS 2, respectively) in the randomly divided two subgroups (groups 1 and 2) to predict the FSGS disease progression. We have cross-validated RS between two groups and found that RS 1 is a better predictive model for discrimination for FSGS disease progression. We further stratified the risk factors into four risk subgroups to assess the performance of the established predictive model RS 1. KM survival curve revealed that renal survival in FSGS patients decreased as risk levels increased, suggesting that RS 1 predicts the disease progression in FSGS patients. In this study, we have developed and validated the first predictive model in FSGS patients which can accurately predict the renal survival in FSGS patients and provide clinician with a better tool to guide them to manage FSGS patients based on different risk categories.

The pathogenesis of FSGS is very complexed. It is known that genetic and environmental factors contributed to the onset and progression of FSGS. Clinical and pathological features in FSGS patients are varied, and their renal endpoints are drastically different. Pathogenesis of PFSGS is thought to be caused by circulating permeability factor (likely cytokines) leading to podocyte injury [33], in which diffuse foot process effacement is present, accompanied by

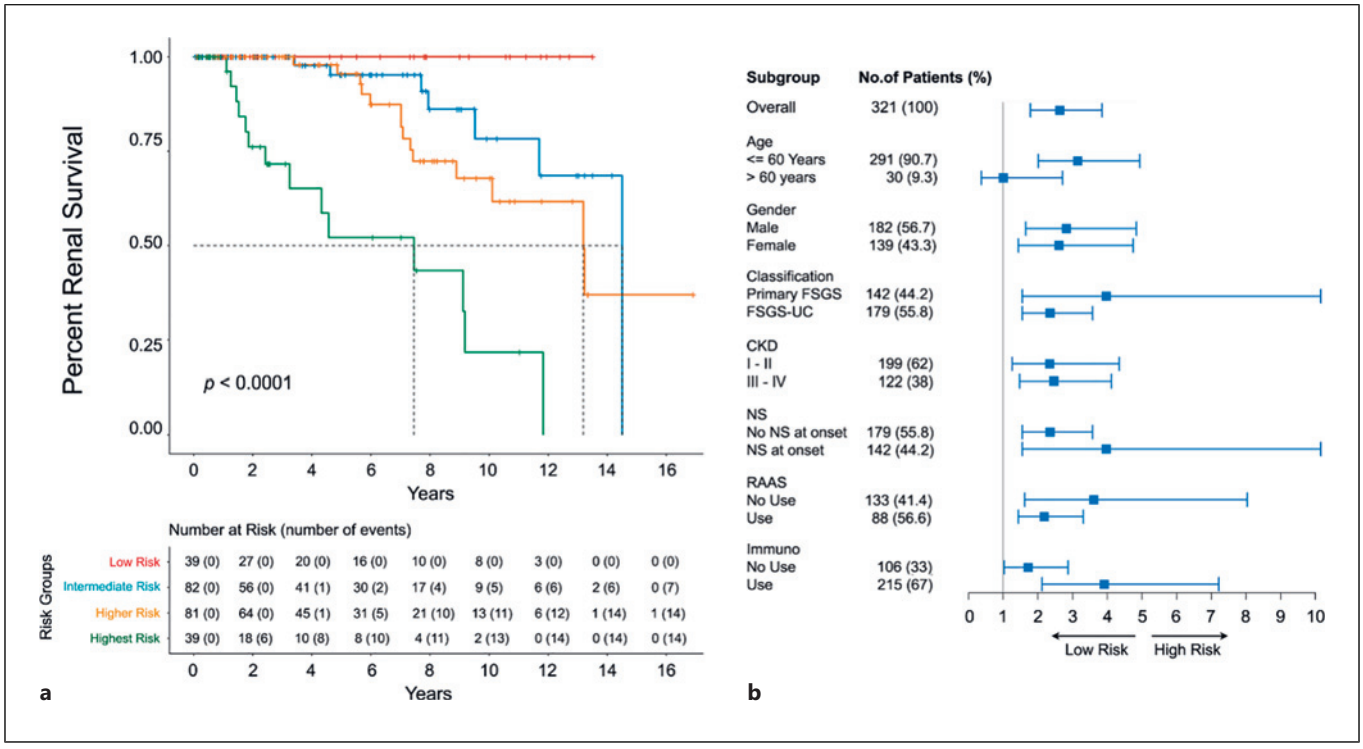

Fig. 4. Kaplan-Meier curves of renal survival in different risk groups and comparison of risk factors in primary renal outcome. **a** Renal survival was calculated based on reaching ESKD. Risk groups were divided into four groups on the basis of percentiles of the linear predictor (low risk: <16th; intermediate risk: 16th to 50th; higher risk: 50th to 84th; and highest risk: >84th). **b** Hazard ratio was derived from Cox analysis in different subgroups. CKD, chronic kidney disease; NS, nephrotic syndrome; RAAS, renin-angiotensin-aldosterone system blocker; Immuno, immunosuppressive agents.

NS and amenable to therapy. Genetic FSGS can be familiar or sporadic [33]. FSGS-UC is a new classification of FSGS in KDIGO 2021 guideline, in which renal biopsy revealed segmental foot process effacement with proteinuria, but without NS and identifiable underlying cause [6, 33].

The progression rate of FSGS to ESKD has recently shown to be increased [2, 11, 34]. Previous studies reported that impaired renal function, hypertension, and large amount of proteinuria upon diagnosis [34–36] as well as not response to the treatments of steroid and immunosuppressive agents were associated with progressive diseases and poor renal survival in patients with FSGS [13, 20, 34, 37, 38]. In addition, progression of FSGS disease was shown to be associated with different pathological features based on the Columbia FSGS classification [19], in which collapsing FSGS had a poorer renal survival rate and much rapid progression to ESKD compared to patients with NOS and tip variant with best renal survival rate in tip variant [11, 20, 38, 39]. However, a recent study reported no significant difference in the progression of ESKD among different pathological FSGS variants [21]. Although previous studies achieved a significant progress in the assessment of the risk prognosis association for FSGS patients, it remains lack of better predictive model for disease progression in FSGS patients.

In the present study, we analyzed the risk factors incorporating new KDIGO classifications of FSGS [6] and developed and validated predictive model for accurately assessing the renal prognosis in our large cohort of Chinese FSGS patients. We established predictive models RS 1 and RS 2 for group 1 and group 2, respectively, through multivariate regression analysis. We cross-validated RS 1 and RS 2 in these two groups. We found that RS 1 consisting of eGFR, UP, MAP, serum IgG, and TIL score had better performance in predicting 3-year and 5-year risk of progression to ESKD compared to RS 2 consisting of MAP, serum IgG, C3, Hb, and TIL score. Our results indicated that lower eGFR, higher UP, higher MAP, higher serum IgG, and higher TIL scores were associated with poor renal outcome in both groups 1 and 2. RS 2 also showed additional risk factors (lower C3 and higher Hb)

that are associated with poor renal outcome in group 2. The lower baseline renal function (lower eGFR), higher UP, higher blood pressure (higher MAP), more severe TIL are found to be associated with worse renal outcomes in the present study, which are consistent with previous reports [13, 20, 22–24, 37, 38]. We also found higher IgG level is associated with poor renal outcome for the first time. It remains not entirely clear why higher IgG level is associated with poor renal outcome which was not previously reported. One of the potential mechanisms underlying this could be over reactivation of immune system to inflammatory process that could reflect the higher immunoreaction to infection and/or inflammation causing more injuries and leading to more fibrosis and poor renal outcome. In addition, RS 2 showed that lower C3 level is a risk factor for disease progression in FSGS patients, which is consistent with our previous finding [40]. Activation of complement system is found to be involved in the pathogenesis of FSGS. Lower C3 level reflected the activation of complement cascade which could lead to inflammation and renal fibrosis, leading to disease progression in FSGS patients.

Previous studies also demonstrated that genetic variants are associated with development of FSGS. More than 60 gene variants or mutations including but limited to *PAX2, ACTN4,* inverted formin 2 (*INF2*), *TRPC6, COL4A3/4/5,* etc., were found so far to be associated with causation of FSGS [41, 42]. Kopp et al. [43] reported that SNPs in myosin heavy chain 9 (*MYH9*) gene were associated with developments of FSGS and HIV-1-associated FSGS in African American patients. Genovese et al. [44] also found that *APOL1* variants (G1 and G2) are strongly associated with development of FSGS only in African American population, suggesting that pathogenicity of FSGS is varied in different races. Our previous study also found that S85W mutation in *INF2* gene was associated with development of FSGS in Chinese population. The overall frequency of *INF2* mutations was ~3.6% among Chinese familial FSGS, which was considerably lower than that from studies of European FSGS families [42]. In the present study, we did not include the information of genetic variants for developing the predictive model, which requires a further study.

Risk predictive model for estimating the real renal outcome has become more popular in recent years that provide clinicians with a tool in their clinical decision-making. Previous studies reported that several predictive models were developed for assessing the risk of prevalent and incident CKD and ESKD with good discriminative performance [32, 45–48], but they have not always performed well in external cohorts [49]. In the present study, we found AUC for predicting 3-year ESKD of 0.95 (95% CI 0.89–0.99) with R^2 of 0.82 and 5-year ESKD of 0.86 (95% CI 0.76–0.96) with R^2 of 0.82 in our whole cohort using RS 1 predictive model, suggesting that RS 1 can better predict the risks for ESKD with high discrimination. Tangri et al. [32] reported that a predictive model for CKD progression was developed from two independent Canadian cohorts. We did ROC curve analysis by comparing the JAMA predictive model reported by Tangri et al. [32] to our RS 1 and RS 2 models and found that both AUC values were higher at 3 years and 5 years using RS 1 and RS 2 than AUCs using the JAMA model, implying that our predictive models RS 1 and RS 2 are the better models in estimating the risks for both 3-year and 5-year ESKD in our FSGS cohort.

In the present study, we further stratified the risks to four different risk groups from our cohort to evaluate the performance of the RS 1 predictive model. KM curve showed that survival curves were well separated between different risk groups and patients progressed to ESKD increased as risk levels increased, suggesting a very good clinical utility to guide clinical decision-making for patients with FSGS. We further confirmed that FSGS patients with male gender, FSGS-UC classification, advanced CKD stages (III-IV) at diagnosis, without NS upon onset, without using renin-angiotensin-aldosterone system inhibitor, and with using immunosuppressive agents have higher risks for progression of diseases with poor renal outcomes.

There are several limitations to the present study. First, this was a single-center study; thus, our RSs need to be externally validated before it can be extended to clinical use; second, all the variables tested in our study were variables obtained at renal biopsy, incorporating variables during follow-up such as time average proteinuria may increase the performance of our RS. The advantage of not including follow-up parameters is that the prognosis of the patient can be predicted at the same time as the kidney biopsy before making treatment decisions; third, in our study we did not include ultrastructural changes such as podocytopathies for establishing RS model due to incomplete pathological information of electronic microscopy despite its potential association with disease progression. We only included the TILs for analysis, which is the limitation in the study. Inclusion of more podocytopathic features for analysis may strengthen the accuracy of the predictive model. Nevertheless, our RS models demonstrated the accurate predictive model in assessing the progression of diseases in patients with FSGS; lastly, only clinical information and pathological feature were used for analysis to develop the predictive model for assessing the renal outcome without incorporating information of different races, genetic variations, and biomarkers. A future multicenter study including genetic mutations, biomarkers, and more diversity of race and ethnic

backgrounds for analysis will be essential to validate this model using the independent external cohorts, which will further increase the accuracy of this predictive model.

In summary, we have successfully developed and validated a RS that is able to accurately predict the risks for ESKD in FSGS patients. We believe that this predictive model can guide clinician to make a sound clinical decision based on different levels of risks to appropriately manage patients with FSGS and enhance their abilities to lead for a better outcome.

Statement of Ethics

This study protocol was reviewed and approved by the Ethics Committee of the Shanghai Jiao Tong University Affiliated Ruijin Hospital (approval number: 2012-39), which was consistent with the Declaration of Helsinki. Written informed consent was obtained from all patients for participation in this study. All authors gave their consent for publication.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest that related to this article.

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Author Contributions

J. Xie and H. Ren designed the study; Y. Cai, Y. Liu, J. Tong, Y. Jin, J. Liu, X. Hao, Y. Ji, J. Ma, and X. Pan collected the data; Y. Cai and Y. Liu analyzed the data; Y. Cai, J. Tong, J. Xie, and H. Ren drafted and revised the paper; N. Chen revised the paper. All authors approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Rosenberg AZ, Kopp JB. Focal segmental glomerulosclerosis. Clin J Am Soc Nephrol. 2017;12(3):502–17.
2 Kitiyakara C, Kopp JB, Eggers P. Trends in the epidemiology of focal segmental glomerulosclerosis. Semin Nephrol. 2003;23(2):172–82.
3 Gipson DS, Trachtman H, Kaskel FJ, Greene TH, Radeva MK, Gassman JJ, et al. Clinical trial of focal segmental glomerulosclerosis in children and young adults. Kidney Int. 2011;80(8):868–78.
4 Fogo AB. Causes and pathogenesis of focal segmental glomerulosclerosis. Nat Rev Nephrol. 2015;11(2):76–87.
5 De Vriese AS, Wetzels JF, Glassock RJ, Sethi S, Fervenza FC. Therapeutic trials in adult FSGS: lessons learned and the road forward. Nat Rev Nephrol. 2021;17(9):619–30.
6 Rovin BH, Adler SG, Barratt J, Bridoux F, Burdge KA, Chan TM, et al. Executive summary of the KDIGO 2021 guideline for the management of glomerular diseases. Kidney Int. 2021;100(4):753–79.
7 McGrogan A, Franssen CF, de Vries CS. The incidence of primary glomerulonephritis worldwide: a systematic review of the literature. Nephrol Dial Transpl. 2011;26(2):414–30.
8 Parsa A, Kao WH, Xie D, Astor BC, Li M, Hsu CY, et al. APOL1 risk variants, race, and progression of chronic kidney disease. N Engl J Med. 2013;369(23):2183–96.
9 Hou JH, Zhu HX, Zhou ML, Le WB, Zeng CH, Liang SS, et al. Changes in the spectrum of kidney diseases: an analysis of 40,759 biopsy-proven cases from 2003 to 2014 in China. Kidney Dis. 2018;4(1):10–9.
10 Scialla JJ, Astor BC, Isakova T, Xie H, Appel LJ, Wolf M. Mineral metabolites and CKD progression in African Americans. J Am Soc Nephrol. 2013;24(1):125–35.
11 Thomas DB, Franceschini N, Hogan SL, Ten Holder S, Jennette CE, Falk RJ, et al. Clinical and pathologic characteristics of focal segmental glomerulosclerosis pathologic variants. Kidney Int. 2006;69(5):920–6.
12 Korbet SM. Clinical picture and outcome of primary focal segmental glomerulosclerosis. Nephrol Dial Transpl. 1999;14(Suppl 3):68–73.
13 Troost JP, Trachtman H, Nachman PH, Kretzler M, Spino C, Komers R, et al. An outcomes-based definition of proteinuria remission in focal segmental glomerulosclerosis. Clin J Am Soc Nephrol. 2018;13(3):414–21.
14 Troyanov S, Wall CA, Miller JA, Scholey JW, Cattran DC; Toronto Glomerulonephritis Registry Group. Focal and segmental glomerulosclerosis: definition and relevance of a partial remission. J Am Soc Nephrol. 2005;16(4):1061–8.
15 Gipson DS, Chin H, Presler TP, Jennette C, Ferris ME, Massengill S, et al. Differential risk of remission and ESRD in childhood FSGS. Pediatr Nephrol. 2006;21(3):344–9.
16 Chun MJ, Korbet SM, Schwartz MM, Lewis EJ. Focal segmental glomerulosclerosis in nephrotic adults: presentation, prognosis, and response to therapy of the histologic variants. J Am Soc Nephrol. 2004;15(8):2169–77.

17 Troost JP, Trachtman H, Spino C, Kaskel FJ, Friedman A, Moxey-Mims MM, et al. Proteinuria reduction and kidney survival in focal segmental glomerulosclerosis. Am J Kidney Dis. 2021;77(2):216–25.
18 Hao X, Xie J, Ma J, Wang Z, Zhou Q, Yang L, et al. Increased risk of treatment failure and end-stage renal disease in familial focal segmental glomerular sclerosis. Contrib Nephrol. 2013;181:101–8.
19 D'Agati VD, Fogo AB, Bruijn JA, Jennette JC. Pathologic classification of focal segmental glomerulosclerosis: a working proposal. Am J Kidney Dis. 2004;43(2):368–82.
20 Tsuchimoto A, Matsukuma Y, Ueki K, Tanaka S, Masutani K, Nakagawa K, et al. Utility of Columbia classification in focal segmental glomerulosclerosis: renal prognosis and treatment response among the pathological variants. Nephrol Dial Transpl. 2020;35(7):1219–27.
21 Kawaguchi T, Imasawa T, Kadomura M, Kitamura H, Maruyama S, Ozeki T, et al. Focal segmental glomerulosclerosis histologic variants and renal outcomes based on nephrotic syndrome, immunosuppression and proteinuria remission. Nephrol Dial Transpl. 2022;37(9):1679–90.
22 Stokes MB, Valeri AM, Markowitz GS, D'Agati VD. Cellular focal segmental glomerulosclerosis: clinical and pathologic features. Kidney Int. 2006;70(10):1783–92.
23 Bazzi C, Petrini C, Rizza V, Arrigo G, D'Amico G. A modern approach to selectivity of proteinuria and tubulointerstitial damage in nephrotic syndrome. Kidney Int. 2000;58(4):1732–41.
24 Shiiki H, Nishino T, Uyama H, Kimura T, Nishimoto K, Iwano M, et al. Clinical and morphological predictors of renal outcome in adult patients with focal and segmental glomerulosclerosis (FSGS). Clin Nephrol. 1996;46(6):362–8.
25 Mariani LH, Martini S, Barisoni L, Canetta PA, Troost JP, Hodgin JB, et al. Interstitial fibrosis scored on whole-slide digital imaging of kidney biopsies is a predictor of outcome in proteinuric glomerulopathies. Nephrol Dial Transpl. 2018;33(2):310–8.
26 Barisoni L, Troost JP, Nast C, Bagnasco S, Avila-Casado C, Hodgin J, et al. Reproducibility of the NEPTUNE descriptor-based scoring system on whole-slide images and histologic and ultrastructural digital images. Mod Pathol. 2016;29(7):671–84.
27 D'Agati V. Pathologic classification of focal segmental glomerulosclerosis. Semin Nephrol. 2003;23(2):117–34.
28 Prayaga AK, Anuradha SV, Manjusha Y, Uppin M, Rapur R, Dakshina Murthy KV. Morphologic evaluation of renal function using semi-quantitative method in primary nonproliferative glomerular diseases. Indian J Pathol Microbiol. 2011;54(1):42–6.
29 Xie J, Lv J, Wang W, Li G, Liu Z, Chen H, et al. Kidney failure risk prediction equations in IgA nephropathy: a multicenter risk assessment study in Chinese patients. Am J Kidney Dis. 2018;72(3):371–80.
30 Barbour SJ, Coppo R, Zhang H, Liu ZH, Suzuki Y, Matsuzaki K, et al. Evaluating a new international risk-prediction tool in IgA nephropathy. JAMA Intern Med. 2019;179(7):942–52.
31 Royston P, Altman DG. External validation of a Cox prognostic model: principles and methods. BMC Med Res Methodol. 2013;13:33.
32 Tangri N, Stevens LA, Griffith J, Tighiouart H, Djurdjev O, Naimark D, et al. A predictive model for progression of chronic kidney disease to kidney failure. JAMA. 2011;305(15):1553–9.
33 De Vriese AS, Sethi S, Nath KA, Glassock RJ, Fervenza FC. Differentiating primary, genetic, and secondary FSGS in adults: a clinicopathologic approach. J Am Soc Nephrol. 2018;29(3):759–74.
34 D'Agati VD, Kaskel FJ, Falk RJ. Focal segmental glomerulosclerosis. N Engl J Med. 2011;365(25):2398–411.
35 Korbet SM, Schwartz MM, Lewis EJ. Primary focal segmental glomerulosclerosis: clinical course and response to therapy. Am J Kidney Dis. 1994;23(6):773–83.
36 Rydel JJ, Korbet SM, Borok RZ, Schwartz MM. Focal segmental glomerular sclerosis in adults: presentation, course, and response to treatment. Am J Kidney Dis. 1995;25(4):534–42.
37 Tang X, Xu F, Chen DM, Zeng CH, Liu ZH. The clinical course and long-term outcome of primary focal segmental glomerulosclerosis in Chinese adults. Clin Nephrol. 2013;80(2):130–9.
38 D'Agati VD, Alster JM, Jennette JC, Thomas DB, Pullman J, Savino DA, et al. Association of histologic variants in FSGS clinical trial with presenting features and outcomes. Clin J Am Soc Nephrol. 2013;8(3):399–406.
39 Ossareh S, Yahyaei M, Asgari M, Bagherzadegan H, Afghahi H. Kidney outcome in primary focal segmental glomerulosclerosis (FSGS) by using a predictive model. Iran J Kidney Dis. 2021;15(6):408–18.
40 Liu J, Xie J, Zhang X, Tong J, Hao X, Ren H, et al. Serum C3 and renal outcome in patients with primary focal segmental glomerulosclerosis. Sci Rep. 2017;7(1):4095.
41 Groopman EE, Povysil G, Goldstein DB, Gharavi AG. Rare genetic causes of complex kidney and urological diseases. Nat Rev Nephrol. 2020;16(11):641–56.
42 Xie J, Hao X, Azeloglu EU, Ren H, Wang Z, Ma J, et al. Novel mutations in the inverted formin 2 gene of Chinese families contribute to focal segmental glomerulosclerosis. Kidney Int. 2015;88(3):593–604.
43 Kopp JB, Smith MW, Nelson GW, Johnson RC, Freedman BI, Bowden DW, et al. MYH9 is a major-effect risk gene for focal segmental glomerulosclerosis. Nat Genet. 2008;40(10):1175–84.
44 Genovese G, Friedman DJ, Ross MD, Lecordier L, Uzureau P, Freedman BI, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. Science. 2010;329(5993):841–5.
45 Tangri N, Grams ME, Levey AS, Coresh J, Appel LJ, Astor BC, et al. Multinational assessment of accuracy of equations for predicting risk of kidney failure: a meta-analysis. JAMA. 2016;315(2):164–74.
46 Chien KL, Lin HJ, Lee BC, Hsu HC, Lee YT, Chen MF. A prediction model for the risk of incident chronic kidney disease. Am J Med. 2010;123(9):836–46.e2.
47 O'Seaghdha CM, Lyass A, Massaro JM, Meigs JB, Coresh J, D'Agostino RB Sr, et al. A risk score for chronic kidney disease in the general population. Am J Med. 2012;125(3):270–7.
48 Kshirsagar AV, Bang H, Bomback AS, Vupputuri S, Shoham DA, Kern LM, et al. A simple algorithm to predict incident kidney disease. Arch Intern Med. 2008;168(22):2466–73.
49 Fraccaro P, van der Veer S, Brown B, Prosperi M, O'Donoghue D, Collins GS, et al. An external validation of models to predict the onset of chronic kidney disease using population-based electronic health records from Salford, UK. BMC Med. 2016;14:104.